Barcoding stem cells: surprises, challenges, and perspectives

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Award: New Innovator Award
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The basic understanding of how tissues are normally maintained by their resident stem cells is key for pursuing regenerative medicine approaches. Though a great deal of knowledge has been gained through the use of traditional experimental approaches over the past two decades, limitations and drawbacks of these techniques have precluded us from gaining a complete understanding of regenerative processes, particularly in the in vivo setting. The goal of my New Innovator proposal was to develop a novel experimental paradigm for the study of stem cell biology and tissue dynamics. In our model, individual stem cells in a population can be uniquely and genetically tagged *in situ* without any sort of perturbation. These genetic tags, or barcodes, are then used to systematically and quantitatively monitor the dynamics, lifespan, and differentiation of thousands of stem cells at the single cell level in highly complex populations over time. We have initially applied this technology to provide unprecedented insight into the biology of the unperturbed blood- and immune-forming systems. Our results challenge the prevailing stem cell-centric dogma in the field, which indicated that a small number of hematopoietic stem cells (HSCs) drive stable and multi-lineage blood-production. Our data instead demonstrate that long-term hematopoiesis is maintained by the successive recruitment of thousands of clones, derived not from HSCs, but from multipotent progenitor cells, a population traditionally thought to have a very restricted lifespan. Our clonal tracing system reveals that these progenitors can be tremendously long-lived and predominantly produce lineage-restricted progeny. Our data argue for a re-evaluation of typical cellular hierarchies in the hematopoietic tree, and have significant implications for understanding the cellular origin of hematopoietic disease. The modular nature of our system should enable cell-type specific transposition, of multiple other lineage and cell populations, paving the way for future systematic and high-resolution analysis of clonal dynamics during development, aging, and multiple biological processes.